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HHMI research team finds hormone that regulates fat storage and energy expenditure

Researchers at the Howard Hughes Medical Institute at Rockefeller University have discovered a new hormone produced by fat tissue and presumably acting on the brain to regulate weight.

The scientists suggest that the mouse obese gene produces a signal that tells the brain that the body's fat stores are sufficient enough to decrease food intake and/or increase energy expenditure.

When mutated in mice, the *obese* gene no longer delivers its appetite-suppressing message to the brain and the mice develop a syndrome that resembles extreme obesity and type II diabetes in humans, said Jeffrey M. Friedman, an investigator with the Howard Hughes Medical Institute at Rockefeller University. Friedman's team has also found the human equivalent of the mouse *obese* gene. The study, published in the December 1, 1994 issue of *Nature*, was co-authored by Yiyang Zhang, Ricardo Proenca, Margherita Maffei, Marisa Barone and Lori Leopold.

Prior research had identified five separate genetic mutations that could cause mice to become overweight. Scientists have known since 1950 that mutations in *obese* could lead to weight gain, but they have been unable to explain how this happens.

Friedman's research suggests that a mutant mouse's obesity is due to a faulty signal, resulting in a mouse that is three times heavier than normal. "This normal signal is absent and the mice continue to eat," Friedman said. He speculates that the obese signal directly or indirectly targets the hypothalamus — the brain command post for appetite — to regulate the size of the body fat depot.

Friedman's laboratory has been trying to uncover the molecular factors that govern obesity for eight years. Their success in cloning *obese* and identifying its human equivalent ends one phase of an intense international search for a blood-borne factor that influences weight gain. "At times this was a very nerve-wracking and exhausting search," Friedman said.

In February, Rockefeller University announced that Amgen, a California biotechnology company, had licensed the rights to the obesity gene for an initial payment of \$20 million and future milestone payments of several times that amount.

Friedman's team is now pursuing further studies to define the nature of the obese signal. They are also searching for the obese receptor, encoded by a second gene called *db*, short for *diabetes*, which Friedman believes is a key to future efforts to target "smarter" drugs to combat obesity.